UCRL-JC-125693 Abs

Benzene metabolism and macromolecular binding in mice at doses relevant for human exposures. Mani, C. and Turteltaub, K.W.
Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94143-0446 and Molecular and Structural Biology Program, Lawrence Livermore National Laboratory, Livermore CA 94551.

Benzene, a rodent and human carcinogen, is a chemical to which humans are exposed both occupationally and environmentally at low doses. The metabolism and adduct formation of [^{14}C] benzene in B6C3F$_1$ and C57BL/6 mice (5ng/kg to 500 mg/kg) is being investigated using the technique of accelerator mass spectrometry. These studies will help to determine the dose relevence of high dose tumor studies for estimating benzene cancer risk at low dose. Peak DNA and protein adducts, following a dose of 5 μg/kg body weight benzene, are found at 1 hr in the liver and at 12 hrs in the bone marrow. Protein and DNA adduct formation in the liver is linear with dose between 500 ng/kg and 50 mg/kg while macromolecular adducts in bone marrow is linear with dose between 500ng/kg and 500 mg/kg. The binding of benzene to hepatic DNA and protein were lower in the liver of the tumor insensitive C57BL/6 mice than in the tumor sensitive B6C3F$_1$ mice. While adduct formation appears to be linear with dose, benzene metabolite profiles in urine are highly dose dependent. At high benzene doses, muconic acid is the major metabolite in urine while at lower doses muconic acid, catechol sulfate and an unknown metabolite are the major urinary metabolites. These results suggest that macromolecular binding is linear with dose below 50 mg/kg, that urinary metabolites are not linear with dose and that adduct levels are related to tumor sensitivity among rodent strains. This work performed under the auspices of the US DOE by LLNL (W-7405-ENG-48) and partially supported by NIH (ES04705) and the Health Effects Institute (#94-5).

AACR
4/12-4/16/97
San Diego CA